



# PROBIOTICS AND PREBIOTICS

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## ABSTRACT

The human gut contains 10 times more bacteria than cells elsewhere in human body. The enormous biomass consists of over 400 known bacterial species that generate intense metabolic activity and are of key importance for human health. Resident microbiota actively contributes to host protection through: blocking of colonization by pathogens, development of cell structure and function, development of the immune system and modulation of inflammatory responses, commensal bacteria influence expression of mediators such as intracellular adhesion molecule I (ICAM-I), E-selectin, and Interleukin (IL-8), commensal bacteria also modulate immune responses and enhance cellular homeostatic mechanisms.<sup>1</sup> This ecosystem gets disrupted when exposed to toxic substances in the form of polluted water and food as well as injudicious use of antibiotics. Antibiotic resistance, with the emergence of multiple resistant strains, is an increasingly important global problem. This causes destruction of beneficial bacteria leaving behind resistant, pathogenic bacteria.<sup>1</sup> With the number of bacteria-resistant diseases on the rise and the length of time it takes to develop new antibiotics, it might be time to consider another alternative, for eg. the use of beneficial bacteria, the 'Probiotics', which stimulate health promoting indigenous flora and reverting back the change, in the treatment of periodontal disease.<sup>2</sup>

**KEYWORDS:** Probiotics, prebiotics, synbiotics, immunity.

## INTRODUCTION:

Periodontics has entered the saga of metamorphosis that explores and understands human body mechanisms at biomolecular levels.<sup>1</sup> With the number of bacteria-resistant diseases on the rise and the length of time it takes to develop new antibiotics, it might be time to consider another alternative, for eg. the use of beneficial bacteria, 'Probiotics', which stimulate health- promoting indigenous flora and reverting back the change, in the treatment of periodontal disease.<sup>2</sup> The term 'probiotic' is derived from the Greek word, meaning "for life."<sup>1</sup>

In their joint report on probiotics published in 2001, the Food and Agriculture Organization of the United Nations and the World Health Organization (FAO/WHO) defined Probiotics as "live microorganisms, which when administered in adequate amounts, confer a health benefit on the host".<sup>10</sup> An International Life Science Institute Europe consensus document proposed a simple and widely accepted definition of probiotics as "viable microbial food supplements which beneficially influence the health of human".

## Prebiotics:

The term prebiotic was introduced by Gibson and Roberfroid. They defined prebiotic as a "non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon."<sup>13</sup> Prebiotics are non-digestible food ingredients (oligosaccharides) which include:- inulin, fructo-oligosaccharides (FOS), Galacto-oligosaccharide, lactulose, Malto-oligosaccharides and resistant starch (Gibson et al, 1995), that affect the proliferation of resident commensal bacteria, which may exert beneficial effects on the host.

## Synbiotics:

Appropriate combinations of prebiotics and probiotics are synbiotics. Synbiotics is the word coined for the combined administration of specific prebiotics with probiotics to provide definite health benefits by synergistic action. As probiotics are mainly active in the small intestine and prebiotics are only effective in the large intestine, the combination of the two may give a synergistic effect.

## List Of Different Microorganisms Used As Probiotics

### A. Bacteria

#### B. *Lactobacillus* spp

*Lactobacillus acidophilus*, *Lactobacillus bulgaricus*, *Lactobacillus casei*, *Lactobacillus crispatus*, *Lactobacillus fermentum*, *Lactobacillus gasseri*

#### II. *Bifidobacterium* spp:

*Bifidobacterium adolescentis*, *Bifidobacterium animalis*, *Bifidobacterium bifidum*, *Bifidobacterium infantis*, *Bifidobacterium lactis*

#### III. *Streptococcus* spp:

*Streptococcus lactis*, *Streptococcus cremoris*, *Streptococcus salivarius*,

*Streptococcus intermedius*

## IV. Others

*Leuconostoc*, *Pedococcus*,

*Propionibacterium*, *Bacillus*, *Clostridium butyricum*, *Enterococcus*, *E. faecium*

## B. Yeast And Moulds

*Ceresvisiae*, *A. Niger*, *A. Oryzue*, *C. Pintolopesii*, *Sacharomyces boulardii* (a non-pathogenic strain of yeast)<sup>16</sup>

**Mechanism of action of probiotics:** Probiotics can help prevent and treat disease through several mechanisms:-

- Direct interaction-** Probiotics interact directly with the disease-causing microbes, making it harder for them to cause the disease.
- Competitive exclusion-** Beneficial microbes directly compete with the disease, developing microbes for nutrition or enterocyte adhesion sites.
- Modulation of host immune response-** Probiotics interact with and strengthen the immune system and help prevent disease. Probiotics stimulate dendritic cells (antigen presenting cells) resulting in expression of helper T cell (Th1) response, which modulates immunity.
- Modulation of cell proliferation and apoptosis** through cell responses to, for example, microbially produced short chain fatty acids.
- Antioxidant production** - Probiotics are also known to produce antioxidants, which in turn prevent plaque formation by neutralizing the free electrons which are needed for the mineralization of plaque.
- Improvement of intestinal barrier integrity** and up-regulation of mucin production.

## Mechanism of action of prebiotics:

- Enhance the growth of resident commensal gut bacteria
- Cellobiose downregulates virulence factors of *Listeria monocytogenes*.
- Exerts a direct effect on the host by stimulating expression of IL-10, Interferon, enhancement of immunoglobulin (IgA) secretion, and modulation of inflammatory responses in pathogens.<sup>15</sup>

## Role of probiotics in oral health

**Dental Caries:** *Lactobacillus rhamnosus* GG has been shown to produce a substance with potential inhibitory activity against cariogenic *Streptococcus* spp.<sup>24</sup>

**Periodontal Diseases:** Probiotic bacteria reported to favour periodontal health if they are able to integrate themselves in oral biofilm and inhibit pathogen growth

and metabolism. Colonization of probiotic bacterial strains replaced the bacteria implicated in halitosis and they have prospective application as adjuncts for the prevention and treatment of halitosis.<sup>24</sup>

#### Toll-like receptors and Probiotics:

Probiotics may regulate immune responses by stimulating toll-like receptors (TLRs). Probiotic strains may interfere with the interactions between other pathogenic bacteria and TLRs on epithelial cells (Lan, et al., 2005).

**Immune modulation:** The ability of a probiotic to alter the host microbiota or host MAMP-recognizing molecules could have several beneficial outcomes for the host, including: anti-infectious properties, immune modulatory effects, enhanced barrier functions, metabolic effects, and alterations of intestinal motility or function.<sup>25</sup>

**Role of innate immunity and probiotic action:** Probiotics can induce production of soluble innate defense factors, such as IgA and cytokines and microbicidal defensin proteins by Paneth cells in the crypts of the small intestine (Hooper, et al., 2003).

**Acquired immunity and Probiotics:** Probiotics may modulate the acquired immune response to other antigens in the environment through interactions with the innate immune system.

**Role of host epithelium in probiotic action:** Epithelial cells recognize microorganisms, may recruit dendritic cells into the epithelium within minutes of exposure to a pathogen, may produce different cytokines in response to different commensal bacteria (Lan, et al., 2005).

**Microbial end products for replacing probiotics:** There are potential hazards inherent in administering a dose of live organisms to patients, including the risk of infection. Thus, it may be desirable in some cases to replace live microbes with isolated microbial components or end products. In future, the bioactive molecules present in effective probiotic organisms may be identified, and can be used in their pure forms. End products do not fall within the limits of the designation "probiotic," but, rather, might be identified as "derived from probiotic organisms."<sup>24</sup>

**Reduction of oral malodor using probiotics:** Certain species were found specifically in healthy individuals compared to subjects with halitosis by 16S rRNA clone library study by Kazar et al in 2003. These species are: *Streptococcus salivarius*, *Rothia mucilaginosa* and certain *Eubacterium* species. Candidate selected for reduction of malodor was *Streptococcus salivarius*<sup>25</sup>

**Probiotics in orthodontic treatment:** Cildir et al in (2009) conducted a clinical study with probiotics and found out that daily consumption of fruit yogurt with *Bifidobacterium animalis* subsp. *Lactis* DN -173010 could reduce the salivary levels of mutans streptococci in orthodontic patients with fixed appliances.<sup>25</sup>

#### ROLE OF PROBIOTICS IN PERIODONTICS

**Periodontal disease:** There are currently not many published reports in the English language on the use of probiotics in the treatment of periodontitis. Mucosal immune responses may be invoked by probiotic immunization. Studies of adhesion molecules have shown that superficial cell layers of the gingiva can be affected and can be stimulated to enhance the presence of immune potent cells (Lappin et al. 2003).

**Guided pocket recolonization:** Teethes W et al (2007) showed in a beagle dog model that when beneficial bacteria were applied in periodontal pockets adjunctively after SRP, subgingival recolonization of periodontopathogens was delayed and the degree of inflammation was reduced at a clinically significant level. The study confirmed the hypothesis and provided a proof of concept for a guided pocket recolonization (GPR) approach in the treatment of periodontitis.

**Probing Depth:** Yoshihiro Shimazaki et al (2008) reported that daily intake of lactic acid foods in subjects with generalized deep Probing Depths (PD) or severe Clinical Attachment Level (CAL) was significantly lower than that in subjects with localized deep PD or slight CAL.<sup>27</sup>

**Bleeding gums:** Daily ingestion of *Lactobacillus reuteri* has been known to positively affect the microflora by reducing gum bleeding. The mechanisms suggested are:

- 1) Production of Reuterin (antibacterial substance)
- 2) Ability to block binding of pathogens to host tissue
- 3) Inhibition of proinflammatory cytokines. *W. cibaria* was also found to inhibit biofilm formation.<sup>27</sup>

#### FUTURE PROSPECTS

In field of oral immunology: Probiotics are being used for passive local immunization. For induction of antibodies in the saliva of newborns after artificial colonization with non-pathogenic, probiotic bacterial strain *Escherichia coli* O83.

Genetically modified bacteria (e.g. *S. mutans*) as replacement therapy in dental caries. In food technology: Probiotic and prebiotics in combination are synbiotic functional food.<sup>26</sup>

In Aeronautics and Space technology: Today NASA, USA, carries out research into probiotic food products aimed at enabling humans to live in space. The project is known under the name of Lacmos. Lac is Latin for milk and Mos for Cosmos.<sup>26</sup>

**Designer probiotics:** The term "Patho-Biotechnology" was introduced by Sletor and Hill. It comprises of three basic approaches-

- a. Use of attenuated bacterial pathogens as vaccine
- b. Isolation and purification of pathogen specific immunogenic protein for direct application
- c. Equipping probiotics bacteria with genetic element necessary to overcome stress outside host, inside host and antagonise invading pathogens

Third approach is termed as "designer probiotics". This approach employs probiotics to be engineered to express receptors that mimic structures on their surface. Few studies done are limited to gut, periodontal studies are lacking, but poses a great potential in this field to develop. Designer probiotics have been employed in treatment of HIV, also employs as a novel vaccine delivery vehicle. Improving the stress tolerance profile of probiotic cultures significantly improves tolerance to processing stress and prolongs survival during subsequent storage. This in turn contributes to a significantly larger proportion of the administered probiotics reaching the desired location (e.g., the gastrointestinal tract/periodontium) in a bioactive form.<sup>27</sup>

**Replacement therapy:** The term replacement therapy (also called bacteriotherapy or bacterial interference) is sometimes used interchangeably with probiotics. But it differs from probiotics in following:

1. Effector strain is not ingested and is applied directly on the site of infection.
2. Colonization of the site by the effector strain is essential.
3. Involves dramatic and long-term change in the indigenous microbiota and is directed at displacing or preventing colonization of a pathogen.
4. Have a minimal immunological impact.

While on other hand Probiotics are generally used as:

1. Dietary supplements and are able to exert a beneficial effect without permanently colonizing the site.
2. Rarely dramatic and long-term microbiological change.
3. Exerts beneficial effects by influencing the immune system.

Teughels *et al.* employed this term as probiotics and conducted studies, with application of *Streptococcus salivaris*, *Streptococcus mitis*, *Streptococcus sanguis*, repeatedly on root surfaces after scaling and root planning have resulted in decreased number of periopathogens. It refers to the basic idea of replacing pathogenic bacteria by supplying commensalisms, which have same affinity for tooth surface adherence.<sup>27</sup>

#### SAFETY CONCERNS AND DOSAGES:

Probiotics organisms are classified by the Food and Drug Administration (FDA) as generally regarded as safe (GRAS).

Probiotic microorganisms:

- Should not be pathogenic
- Should not transfer genes responsible for resistance to antibiotics
- Should not act as live vectors for antigen transfer

#### COMMERCIALLY AVAILABLE PROBIOTICS

**Single-strain:** *Saccharomyces boulardii* (Laboratories Biocodex, Montrouge, France): in doses of 2 capsules containing 250 mg equivalent to approximately 10 billion live organisms/d.

- The nonpathogenic *E. coli* serotype O6:K5:H (Nissle 1917) (Mutaflor, Germany) in doses of less than 10 billion/d.
- *Lactobacillus GG* (LG) (Valio, Helsinki, Finland) doses of 1 to 5 billion/d.
- *L. acidophilus* LA1 (LA1) (Nestle, Vevey, Switzerland) in doses of less than 5 billion/d.<sup>27</sup>

**Multi-strain**

- The probiotic cocktail VSL#3 (Sigma-Tau, Italy and VSL Pharmaceuticals, Florida) is the only multistrain probiotic tried so far.
- It consists of 4 *Lactobacillus* strains (*L. acidophilus*, *L. casei*, *L. delbrueckii* subsp. *bulgaricus*, and *L. plantarum*), 3 *Bifidobacterium* strains (*B. longum*, *B. infantis*, *B. breve*), and *S. salivarius* ssp. *thermophilus* (5 1011 cells/g). Dose: 1800 billion bac. and up to 3600 billion B/d.<sup>27</sup>

**STATUS OF PROBIOTICS IN INDIA:**

- Used as animal feed supplements for cattle and poultry.
- Yakult Dannone released their Probiotic drink named Yakult.
- The latest and recent addition to the list of Probiotics in India is **ViBact** (which is made up of genetically modified *Bacillus mesentericus*).
- Probiotic yogurts have been launched by Mother Dairy.

**DISCUSSION:**

Recent research has suggested that consumption of 2 kg/day of Turkish yogurt effectively eliminates biofilm formation on indwelling voice prostheses, possibly related to the presence of *Streptococcus thermophilus* and *Lactobacillus bulgaricus* in Turkish yogurt.<sup>21</sup>

In India, sporolac, *saccharomyces boulardii* and yogurt (*L. bulgaricus* + *L. thermophilus*) are the most common ones used. Sporolac is manufactured using sporolactobacilli. Lactobacilli solution is an example of a probiotic, usually given to pediatric patients. The latest and recent addition to the list of probiotics in India is made up of genetically modified *Bacillus mesentericus* which acts as an alternative to B-complex capsules. Only sporulating lactobacilli are used with some of the antibiotic preparations.<sup>21</sup>

**Koll-Klais et al (2005)** found a prevalence of *Lactobacillus gasseri* and *L. fermentum* in the oral cavity of healthy individuals compared to those with chronic periodontitis.<sup>24</sup>

*Streptococcus oralis* and *Streptococcus uberis* have been shown to inhibit the growth of pathogens both in vitro and in vivo. The presence of these organisms is an indicator of good periodontal health.<sup>27</sup>

**SIDE EFFECTS:**

Excessive consumption of prebiotics particularly those in the oligosaccharides category may cause abdominal discomfort and distension, as well as significant levels of flatulence. The Nutrition Information Centre of South Africa's University of Stellenbosch, recommends that daily consumption of prebiotics be held below 20 grams.<sup>28</sup>

**BOTTLENECKS:**

The probiotic potential of a microbial species is strain specific. It is necessary to identify the strain that exhibits the highest probiotic potential without exhibiting any pathogenic potential. Though many microbes are being studied to assess their probiotic potential, clarity is still lacking in terms of the concentration of the microbes that is needed to elicit a beneficial or inhibitory effect, the duration for which the probiotic has to be administered, and the possibility for the development of resistant strains of bacteria. Another area of concern is the lack of long term studies that assessed whether the administered microbes have the potential to permanently colonise the oral cavity. The time duration for which these probiotics are available (sustainability of the probiotic) in the oral cavity is an important parameter that decides the long term effect of this treatment modality. Studies comparing the effect of probiotics and antibiotics as adjuncts to scaling and root planing and comparing the bioavailability of the probiotic administered in the various formulations are few.<sup>18</sup>

**CONCLUSION**

There has been a paradigm shift towards an ecological and microbial community-based approach to understanding oral diseases. This has significant implications for approaches to therapy and has raised the possibility of developing novel strategies through manipulation of the resident oral microbiota and modulation of host immune responses. Probiotics have become of interest to researchers in recent times. Time has come to shift the paradigm of treatment from specific bacteria elimination to altering bacterial ecology by probiotics. The development of resistance to a range of antibiotics by some important pathogens has raised the possibility of a return to the pre-antibiotic dark ages. Here, probiotics provide an effective alternative way, which is economical and natural to combat periodontal disease. The use of probiotics for use in oral care applications is gaining momentum. There is increasing evidence that the use of existing probiotic strains can deliver oral health benefits.<sup>29</sup>

Thus, a mere change in diet by including probiotic foods may halt, retard, or even significantly delay the pathogenesis of periodontal diseases, promoting a healthy lifestyle to fight periodontal infections. However, randomized controlled trials are needed to assess the best strains, means of administering probiotics and the dosages needed for different preventive or therapeutic purposes. Researches

have confirmed that the diseases of the periodontium are not confined to the oral cavity but have strong systemic effects. Hence a good oral health confers a good systemic state and probiotics offer a natural and promising option to establish this.<sup>29</sup>

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